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(71) Applicant *(for all designated States except US)*: **CEPA SCHWARZ PHARMA, S. L.** [ES/ES]; P° De La Castellana, 141, Planta 15, E-28046 Madrid (ES).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **LÓPEZ RODRÍGUEZ, María Luz** [ES/ES]; C. Rector Hoyo Vilanova, 10, E-28048 Madrid (ES). **BENHAMÚ SALAMA, Bellinda** [ES/ES]; Avda. Valdelaparra, 76, E-28100 Alcobendas (madrid) (ES). **VALHONDO FALCÓN, Margarita** [ES/ES]; C. Digital, 7, E-28024 Madrid (ES).

(74) Agent: **BARLOCCI, Anna**; Zea, Barlocci & Markvardsen, Balmes, 30 1° 1ª, E-08007 Barcelona (ES).

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(54) Title: ARYLPIPERAZINE DERIVATIVES AND USE THEREOF AS 5-HT1A RECEPTOR LIGANDS

(57) Abstract: Novel substituted arylpiperazine derivatives with activity as 5- hydroxytryptamine 1A (5-HT1A) receptor subtype ligands, to their stereochemical isomers, methods of their preparation, and to their use and to pharmaceutical compositions containing them for the treatment of Parkinson disease, cerebral damage by thromboembolic ictus, craneoencephalic traumatisms, depression, migraine, pain, psychosis, anxiety disorders, aggressive disorders or urinary tract disorders.

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ARYLPIPERAZINE DERIVATIVES AND USE THEREOF AS 5-HT1A RECEPTOR LIGANDS

FIELD OF THE INVENTION

The present invention relates to arylpiperazine derivatives and, in particular, to their activity as 5-hydroxytryptamine 1A ($5\text{-}HT_{1A}$) receptor subtype ligands, to their stereochemical isomers and to their use and to pharmaceutical compositions containing them for the treatment of pathological states for which a ligand of these receptors is indicated.

BACKGROUND ART

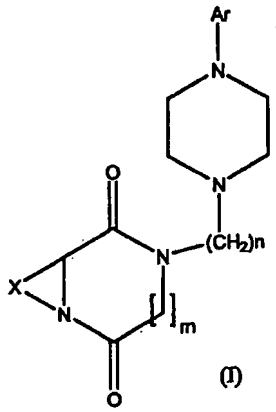
$5\text{-}HT_{1A}$ receptor is a major target for neurobiological research and drug development due to its implication in many (patho)physiological processes. $5\text{-}HT_{1A}$ ligands have been proven to be effective in anxiety and depression. In addition to therapeutic applications in the field of psychiatry, more recent preclinical studies have suggested that $5\text{-}HT_{1A}$ receptor ligands have also pronounced neuroprotective properties.

$5\text{-}HT_{1A}$ ligands may find use in the treatment of several diseases such as anxiety, depression, schizophrenia, sexual dysfunction, cognitive deficits resulting from neurodegenerative diseases like Alzheimer's Disease, nausea and vomiting, sleep disorders, pain, obesity, pain, addiction/withdrawal and in the treatment of prostate cancer. More recent evidence now indicates that $5\text{-}HT_{1A}$ ligands act in other disease states and conditions by virtue of their ability to inhibit the release of glutamate. $5\text{-}HT_{1A}$ ligands may be used to treat conditions arising from the dysfunction of the glutamate neurotransmitter system or the aberrant release of glutamate.

Glutamate is the predominant neurotransmitter in the central nervous system and it plays an important role in neuroplasticity. As such, excessive extracellular levels of glutamate have been associated with the pathophysiology of both acute neurodegenerative disorders such as stroke, transient ischemic attack and spinal/brain trauma, as well as chronic neurodegenerative disorders such as epilepsy, Alzheimer's Disease, amyotrophic lateral sclerosis, Huntington's Disease, Parkinson's Disease, AIDS dementia and retinal diseases. Compounds which inhibit or attenuate

the release of glutamate represent potential neuroprotective agents for the treatment of ischemia resulting from stroke, transient ischemic attack, brain/spinal trauma and fetal hypoxia (Koroshetz, W. J. and Moskowitz, M. A., Emerging Treatment for Stroke in Humans. Trends in Pharmacol. Sci. 1996, 17, 227-233).

WO 96/06846 relates to arylpiperazine derivatives of formula I



(I)

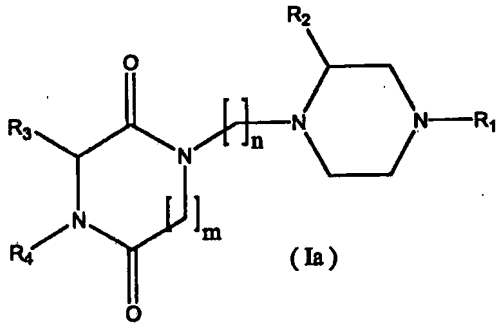
wherein X is $-(CH_2)_3-$ or $-(CH_2)_4-$; m = 0 or 1; n = 1 to 4; Ar = 1-naphthyl, 7-benzofuranyl, 2,3-dihydro-1,4-benzodioxan-5-yl, 3,4-dihydro-2*H*-1,5-benzodioxepin-6-yl, phenyl or phenyl substituted by alkyl, halogen, trifluoromethyl, nitro, cyano, alkoxy or amino.

J. Med. Chem. 1996, 39, 4439, J. Med. Chem. 2001, 44, 186, and Bioorg. Med. Chem. Lett. 2003, 13, 1429 relate to computational simulation and pharmacological characterization of some compounds described in WO 96/06846.

The compounds of the invention, described below, are structurally different from the compounds described in WO 96/06846 because of the novel substituents present on the piperazine ring at the 2 position. These structural variations are neither disclosed nor suggested by WO 96/06846, or in Lopez-Rodriguez et al, J. Med. Chem. 1996, 39, 4439, J. Med. Chem. 2001, 44, 186, and Bioorg. Med. Chem. Lett. 2003, 13, 1429. These structural variations result in compounds that are useful as $5\text{-}HT_{1A}$ ligands, with a remarkable affinity for the serotoninergic $5\text{-}HT_{1A}$ receptor and selectivity over α_1 adrenergic receptors.

SUMMARY OF THE INVENTION

According to the first aspect of the present invention, it provides arylpiperazine derivatives of formula Ia:



(Ia)

wherein:
m is an integer from 0 to 1;
R_3 and R_4 are H or are methylene groups bound together forming with the heterocyclic ring a 5- or 6- membered ring;
n is an integer from 1 to 4;
R_1 is selected from naphth-1-yl; naphth-2-yl, benzodioxepin-6-yl, benzodioxan-4-yl, benzimidazol-4-yl, dihydro-2*H*-1,5-benzodioxan-5-yl, 7-benzofuranyl, tetrahydronaphthyl or phenyl, wherein phenyl, tetrahydronaphthyl and naphtyl are each optionally substituted with one or more groups chosen from (C_1-C_6)-alkoxy, (C_1-C_6)alkyl, halogen, (C_2-C_6)-alkenyl, halo-(C_1-C_6)-alkyl, phenyl, phenyl(C_1-C_6)-alkyl, phenoxy, (C_1-C_6)-alkylcarbonyl, phenylcarbonyl, phenyl(C_1-C_6)alkylcarbonyl, (C_1-C_6)-alkoxycarbonyl, phenyl(C_1-C_6)alkoxycarbonyl, (C_1-C_6)-alkylcarbonylamino, hydroxy, cyano, nitro, amino, carboxy, sulfo, sulfamoyl, sulfonylamino, (C_1-C_6)alkylaminosulfonyl or (C_1-C_6)alkylsulfonylamino; and
R_2 is selected from (C_1-C_4)alkyl, (C_2-C_4)alkenyl, (C_1-C_4)alkoxy, halo-(C_1-C_4)alkyl, halogen, hydroxyl, amino, cyano;
their stereoisomers, N-oxides, crystalline forms, hydrates, pharmaceutically acceptable salts and pharmaceutically acceptable solvates.

A second aspect of the invention relates to a pharmaceutical composition comprising an effective amount of a compound of formula Ia,

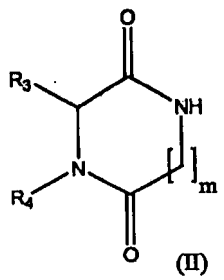
their stereoisomers, N-oxides, crystalline forms, hydrates, pharmaceutically acceptable salts and pharmaceutically acceptable solvates or mixtures in combination with pharmaceutically acceptable carriers. Accordingly, the present invention relates to a pharmaceutical composition as defined above for the treatment and/or prophylaxis of Parkinson Disease, cerebral damage by thromboembolic ictus, craneoencephalic traumatisms, depression, migraine, pain, psychosis, anxiety disorders, aggressive disorders or urinary tract disorders, particularly urinary incontinence.

A third aspect of the invention relates to use of a compound of formula Ia, their stereoisomers, N-oxides, crystalline forms, hydrates, pharmaceutically acceptable salts and pharmaceutically acceptable solvates as described herein, for the manufacture of a medicament for the treatment and/or prophylaxis of Parkinson Disease, cerebral damage by thromboembolic ictus, craneoencephalic traumatisms, depression, migraine, pain, psychosis, anxiety disorders, aggressive disorders or urinary tract disorders, particularly urinary incontinence.

This third aspect may alternatively be formulated as a method for treatment of the diseases mentioned above in a human comprising administering to a human in need thereof an effective amount of pharmaceutical product as described herein.

A fourth aspect of the invention relates to processes for the preparation of the compounds of formula Ia as defined herein which comprises one of the following:

i) reacting a compound of formula II

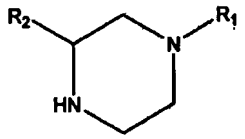


(II)

wherein

m, R_3 and R_4 are as defined in this specification and the claims;

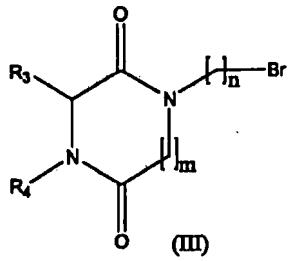
with a compound of formula (IV)



(IV)

wherein R_1 and R_2 are as defined in this specification and the claims;
resulting in final products of formula Ia wherein n = 1;
or

ii) reacting a compound of formula (III)



(III)

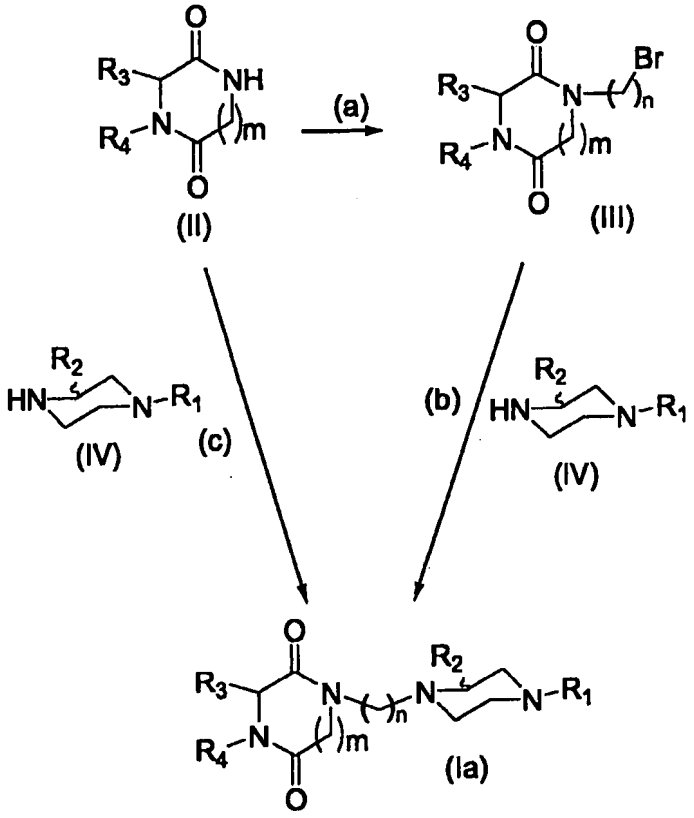
wherein R_3, R_4, and m are as defined in this specification and the claims; and
n > 1;
with a compound of formula (IV) as defined above;
resulting in final compounds of formula Ia wherein n > 1;
or

iii) acidifying a basic compound of formula Ia with a pharmaceutically acceptable acid to give a pharmaceutically acceptable salt;
or

iv) separating a mixture of isomers of a compound of formula Ia to isolate one of such isomers substantially free from the other isomer.

Processes i) and ii) are illustrated in Scheme 1, wherein step c) correspond to process i) and steps a) and b) corresponds to process ii).

Scheme 1.



Scheme 1. Reagents and conditions: (a) Halogen-(CH_2)n-Halogen, NaH, DMF, 110 °C, 1-3 h. (b) NEt_3, CH_3CN, 60 °C, 20 h. (c) HCHO aq, EtOH, reflux, 6 h.

DETAILED DESCRIPTION OF THE INVENTION:

The inventors have surprisingly identified a class of compounds with a high affinity for the 5-HT_{1A} receptor and remarkable neuroprotective properties.

Definitions

Prior to a discussion of the detailed embodiments of the invention is provided a definition of specific terms related to the main aspects of the

invention.

The term "pharmaceutically acceptable salt", as used herein, refers to salts derived from organic and inorganic acids. The compound of the general formula Ia may be converted into its pharmaceutically acceptable salts, or its pharmaceutically acceptable solvates by conventional methods. For example, such salts may be prepared by treating one or more of the compounds with an aqueous solution of the desired pharmaceutically acceptable metallic hydroxide or other metallic base and evaporating the resulting solution to dryness, preferably under reduced pressure in a nitrogen atmosphere. Alternatively, a solution of the compound of formula Ia may be mixed with an alkoxide of the desired metal, and the solution subsequently evaporated to dryness. The pharmaceutically acceptable hydroxides, bases, and alloxides include those worth cations for this purpose, including (but not limited to), potassium, sodium, ammonium, calcium, and magnesium. Other representative pharmaceutically acceptable salts include hydrochloride, hydrobromide, sulphate, bisulphate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, acetate, oxalate, propionate, nitrate, methanesulfonate, benzoate and similarly known acceptable acids.

The term "(C_1-C_4)alkyl" as used herein refers to a saturated branched or linear hydrocarbon chain with 1 to 4 hydrocarbon atoms. Preferably "(C_1-C_4)alkyl" is an unsubstituted group selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, s-butyl and t-butyl.

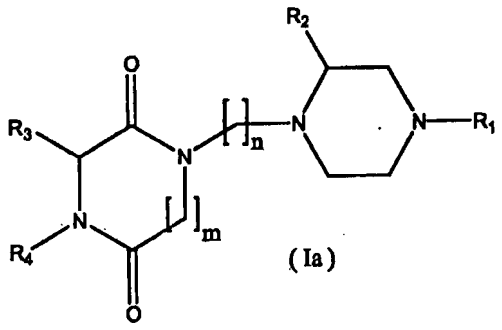
The term "(C_1-C_6)-alkoxy" as used herein refers to a saturated branched or linear hydrocarbon chain with 1 to 6 hydrocarbon atoms (i.e. (C_1-C_6)alkyl groups as defined above) linked to an oxygen, thus (C_1-C_6)alkyl-O. Preferably "(C_1-C_6)-alkoxy" is an unsubstituted group selected from methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, s-butoxy, and t-butoxy.

The term "halogen" is meant to include fluorine, chlorine, bromine and iodine.

It is clear to a person skilled in the art that the compounds of the present invention have at least two optical centers and to thus form "stereoisomers", such as e.g. diastereomers. The racemic forms as well as all optical isomers are part of the present invention and are thus encompassed by the scope of

the claims.

According to the first aspect of the present invention, it provides arylpiperazine derivatives of formula Ia:



(Ia)

wherein:

m is an integer from 0 to 1;

R_3 and R_4 are H or are methylene groups bound together forming with the heterocyclic ring a 5- or 6- membered ring;

n is an integer from 1 to 4;

R_1 is selected from naphth-1-yl; naphth-2-yl, benzodioxepin-6-yl, benzodioxan-4-yl, benzimidazol-4-yl, dihydro-2*H*-1,5-benzodioxan-5-yl, 7-benzofuranyl, tetrahydronaphthyl or phenyl, wherein phenyl, tetrahydronaphthyl and naphtyl are each optionally substituted with one or more groups chosen from (C_1-C_6)-alkoxy, (C_1-C_6)alkyl, halogen, (C_2-C_6)-alkenyl, halo-(C_1-C_6)-alkyl, phenyl, phenyl(C_1-C_6)-alkyl, phenoxy, (C_1-C_6)-alkylcarbonyl, phenylcarbonyl, phenyl(C_1-C_6)alkylcarbonyl, (C_1-C_6)-alkoxycarbonyl, phenyl(C_1-C_6)alkoxycarbonyl, (C_1-C_6)-alkylcarbonylamino, hydroxy, cyano, nitro, amino, carboxy, sulfo, sulfamoyl, sulfonylamino, (C_1-C_6)alkylaminosulfonyl or (C_1-C_6)alkylsulfonylamino; and

R_2 is selected from (C_1-C_4)alkyl, (C_2-C_4)alkenyl, (C_1-C_4)alkoxy, halo-(C_1-C_4)alkyl, halogen, hydroxyl, amino, cyano;

their stereoisomers, N-oxides, crystalline forms, hydrates, pharmaceutically acceptable salts and pharmaceutically acceptable solvates.

According to an embodiment of the first aspect of the invention, it relates to arylpiperazine derivatives according to formula Ia, as defined above, wherein R_3 and R_4 are methylene groups bound together forming with the heterocyclic ring a 5- membered ring.

According to another embodiment of the first aspect of the invention, it relates to arylpiperazine derivatives according to formula Ia, as defined above, wherein R_3 and R_4 are methylene groups bound together forming with the heterocyclic ring a 5- membered ring; and preferably m = 1.

According to another preferred compounds, R_3 and R_4 are methylene groups bound together forming with the heterocyclic ring a 5- membered ring; and preferably m = 0.

According to another preferred embodiment, R_1 is selected from naphth-1-yl, benzimidazol-4-yl, 7-benzofuranyl, benzodioxepin-6-yl, or phenyl, wherein phenyl, and naphtyl are each optionally substituted with one or more groups chosen from (C_1-C_6)-alkoxy, (C_1-C_6)alkyl, nitro, or halogen.

In a more preferred embodiment, R_1 is selected from 3-chlorophenyl, 3-methoxyphenyl, 4-methylnaphth-1-yl, 1-benzofuran-7-yl, naphth-1-yl, benzimidazole-4-yl, 4-nitronapth-1-yl, and phenyl.

In an additional preferred embodiment, R_1 is selected from unsubstituted naphth-1-yl, benzimidazol-4-yl, 1-benzofuran-7-yl and benzodioxepin-6-yl.

In a particularly preferred embodiment of the invention, R_1 is selected from unsubstituted naphth-1-yl, 1-benzofuran-7-yl and benzimidazol-4-yl.

In a more preferred embodiment, R_2 = (C_1-C_4)alkyl, and particularly preferred R_2 represents methyl or ethyl.

Particularly preferred are those compounds wherein R_3 and R_4 are methylene groups bound together forming with the heterocyclic ring a 5-membered ring, m= 0 or 1, n = 1 to 4, R_2=(C_1-C_4)alkyl and particularly preferably methyl or ethyl, and R_1 is selected from naphth-1-yl, benzimidazol-4-yl, 7-benzofuranyl, benzodioxepin-6-yl, or phenyl, wherein phenyl, and naphtyl are each optionally substituted with one or more groups chosen from (C_1-C_6)-alkoxy, (C_1-C_6)alkyl, nitro, or halogen.

According to another embodiment of the invention, n is 1, 3 or 4.

According to a preferred embodiment of the present invention, R_3 and R_4 are methylene groups bound together forming with the heterocyclic ring a 5- membered ring; m = 1; R_1 is selected from unsubstituted naphth-1-yl and benzodioxepin-6-yl; R_2 = (C_1-C_4)alkyl; their stereoisomers, N-oxides, crystalline forms, hydrates, pharmaceutically acceptable salts and pharmaceutically acceptable solvates.

Accordingly, in a more specific embodiment of the present invention, it relates to compounds of formula Ia wherein R_3 and R_4 are methylene groups bound together forming with the heterocyclic ring a 5- membered ring; m = 1; n = 1; R_1 is unsubstituted naphth-1-yl; R_2 = (C_1-C_4)alkyl; their stereoisomers, N-oxides, crystalline forms, hydrates, pharmaceutically acceptable salts and pharmaceutically acceptable solvates.

Furthermore, compounds wherein R_3 and R_4 are methylene groups bound together forming with the heterocyclic ring a 5- membered ring; m = 1; n = 4; R_1 is naphth-1-yl; R_2 = (C_1-C_4)alkyl; their stereoisomers, N-oxides, crystalline forms, hydrates, pharmaceutically acceptable salts and pharmaceutically acceptable solvates, are particularly preferred.

Also, in a preferred embodiment of the present invention, R_3 and R_4 are methylene groups bound together forming with the heterocyclic ring a 5-membered ring; m = 0; R_1 is selected from naphth-1-yl, benzimidazol-4-yl, 7-benzofuranyl, or phenyl, wherein phenyl, and naphtyl are each optionally substituted with one or more groups chosen from (C_1-C_6)-alkoxy, (C_1-C_6)alkyl, nitro, or halogen; R_2 = (C_1-C_4)alkyl; their stereoisomers, N-oxides, crystalline forms, hydrates, pharmaceutically acceptable salts and pharmaceutically acceptable solvates.

Additionally, in a more preferred embodiment of the present invention, R_3 and R_4 are methylene groups bound together forming with the heterocyclic ring a 5- membered ring; m = 0; R_1 is selected from 3-chlorophenyl, 3-methoxyphenyl, 4-methylnaphth-1-yl, 1-benzofuran-7-yl, naphtha-1-yl, benzimidazole-4-yl, 4-nitronapth-1-yl, and phenyl; R_2 = (C_1-C_4)alkyl; their stereoisomers, N-oxides, crystalline forms, hydrates, pharmaceutically

acceptable salts and pharmaceutically acceptable solvates.

Particularly preferred, are those compounds wherein R_3 and R_4 are methylene groups bound together forming with the heterocyclic ring a 5-membered ring; m = 0; n = 3; R_1 is selected from 3-chlorophenyl, 3-methoxyphenyl, and 1-benzofuran-7-yl; R_2 = (C_1-C_4)alkyl; their stereoisomers, N-oxides, crystalline forms, hydrates, pharmaceutically acceptable salts and pharmaceutically acceptable solvates.

Other compounds particularly preferred, are those wherein R_3 and R_4 are methylene groups bound together forming with the heterocyclic ring a 5-membered ring; m = 0; n = 4; R_1 is selected from 3-methoxyphenyl, 4-methylnaphth-1-yl, 1-benzofuran-7-yl, naphtha-1-yl, benzimidazole-4-yl, 4-nitronapth-1-yl, and phenyl; R_2 = (C_1-C_4)alkyl; their stereoisomers, N-oxides, crystalline forms, hydrates, pharmaceutically acceptable salts and pharmaceutically acceptable solvates.

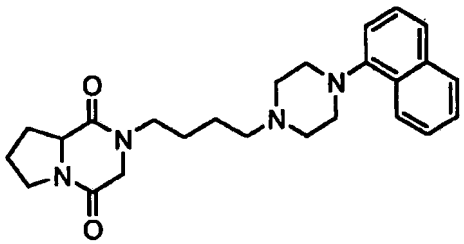
The following compounds are particularly preferred:

(a) (2*R*,8a*RS*)-2-[4-[4-(Naphth-1-yl)-2-methylpiperazin-1-yl]butyl]-1,4-dioxoperhydropyrrolo[1,2-*a*]pyrazine;
(b) (2*S*,8a*RS*)-2-[4-[4-(Naphth-1-yl)-2-methylpiperazin-1-yl]butyl]-1,4-dioxoperhydropyrrolo[1,2-*a*]pyrazine;
(c) (2*R*,8a*R*)-2-[[4-(Naphth-1-yl)-2-methylpiperazin-1-yl]methyl]-1,4-dioxoperhydropyrrolo[1,2-*a*]pyrazine;
(d) (2*S*,8a*S*)-2-[[4-(Naphth-1-yl)-2-methylpiperazin-1-yl]methyl]-1,4-dioxoperhydropyrrolo[1,2-*a*]pyrazine;
(e) (2*R*,8a*S*)-2-[[4-(Naphth-1-yl)-2-methylpiperazin-1-yl]methyl]-1,4-dioxoperhydropyrrolo[1,2-*a*]pyrazine;
(f) (2*S*,8a*R*)-2-[[4-(Naphth-1-yl)-2-methylpiperazin-1-yl]methyl]-1,4-dioxoperhydropyrrolo[1,2-*a*]pyrazine.
(i) (2*R*,7a*RS*)-(-)-2-[3-[4-(3-Chlorophenyl)-2-methylpiperazin-1-yl]propyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole;
(j) (2*S*,7a*RS*)-(+)-2-[3-[4-(3-Methoxyphenyl)-2-methylpiperazin-1-yl]propyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole;
(k) (2*S*,7a*RS*)-(-)-2-[3-[4-(1-Benzofuran-7-yl)-2-methylpiperazin-1-yl]propyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole;

(l) (2*R*,7a*RS*)-(-)-2-[4-[2-Ethyl-4-(naphth-1-yl)piperazin-1-yl]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole;
(m) (2*R*,7a*RS*)-(-)-2-[4-[4-(Benzimidazol-4-yl)-2-methylpiperazin-1-yl]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole;
(n) 2*S*,7a*RS*)-(+)-2-[4-[4-(1-Benzofuran-7-yl)-2-methylpiperazin-1-yl]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole;
(o) (2*R*,7a*RS*)-(-)-2-[4-[2-Ethyl-4-(3-methoxyphenyl)piperazin-1-yl]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole;
(p) (2*S*,7a*RS*)-(+)-2-[4-[2-Methyl-4-(4-methylnaphth-1-yl)piperazin-1-yl]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole;
(q) (2*S*,7a*RS*)-(+)-2-[4-[2-Methyl-4-phenylpiperazin-1-yl]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole;
(r) (2*S*,7a*RS*)-(+)-2-[4-[4-(Benzimidazol-4-yl)-2-methylpiperazin-1-yl]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole;
(s) (2*S*,7a*RS*)-(+)-2-[4-[2-Methyl-4-(4-nitronaphth-1-yl)piperazin-1-yl]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole.

Also, the inventors have discovered some compounds with an unsubstituted piperazine ring but which, compared to the prior art compounds disclosed in the references cited above, have particularly promising pharmacological properties. These compounds do thus also form a part of the invention:

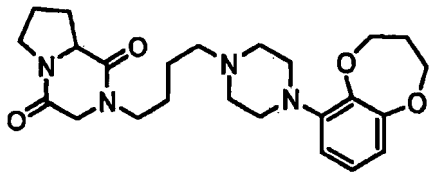
(g) 2-[4-[4-(Naphth-1-yl)piperazin-1-yl]butyl]-1,4-dioxoperhydropyrrolo[1,2-*a*]pyrazine:



Compound (g) binds in the picomolar range to the 5-HT_{1A} receptor and in the low nanomolar range to the α_1 adrenoceptor (see table 1), which makes the compound be a particularly interesting compound for the treatment of e.g. urinary incontinence.

(h) 2-[4-[4-(3,4-Dihydro-2*H*-1,5-benzodioxepin-6-yl)piperazin-1-yl]butyl]-1,4-

dioxoperhydropyrrolo[1,2-a]pyrazine



Compound (h) also binds to the 5-HT_{1A} receptor in the low nanomolar range and also binds in the nanomolar range to the α_1 adrenoceptor. This is surprising because the benzodioxepine derivatives in prior art (Bioorg. Med. Chem. Lett. 2003, 13, 1429) do not show substantial binding to the α_1 receptor.

The final products have been structurally characterized by IR, NMR and quantitative elemental analysis techniques. For greater ease of handling, when the final product is not crystalline, it is transformed in a pharmaceutically acceptable salt, derived from an inorganic or organic acid.

It is understood that compounds according to formula Ia can include asymmetric carbons, and formula Ia encompasses all possible stereoisomers and mixtures thereof, as well as racemic modifications, particularly those that possess the activity discussed below. Optical isomers may be obtained in pure form by standard separation techniques.

Pharmaceutical Product

In other embodiments, the invention provides pharmaceutical compositions containing one or more of the compounds of formula Ia, their stereoisomers, pharmaceutically acceptable salts or pharmaceutically acceptable solvates, and optionally one or more pharmaceutically acceptable carriers, excipients or diluents. The term "carrier", as used herein, shall encompass carriers, excipients and diluents.

Examples of such carriers are well known to those skilled in the art and are prepared accordance with acceptable pharmaceutical procedures. Pharmaceutically acceptable carriers are those carriers that are compatible with the other ingredients in the formulation and are biologically acceptable.

A pharmaceutical product as described herein can be administered orally, transdermally, parenterally, intramuscularly, intravenously, subcutaneously or by other modes of administration. Preferably, the pharmaceutical product can be administered orally.

Representative solid carriers include one or more substance that can act as flavouring agents, lubricants, solubilizers, suspending agents, fillers, glidants, compression aids, binders, tablet-disintegrating agents, or encapsulating materials. Oral formulations containing the active compounds of this invention may comprise any conventionally used oral forms, including tablets, capsules, buccal forms, troches, lozenges and oral liquids, suspensions or solutions. In powders, the carrier is a finely divided solid that is in admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed with a carrier having the necessary compression properties in suitable proportion and compacted in the shape and size desired.

Capsules may contain mixtures of the active compound(s) with inert fillers and/or diluents such as the pharmaceutically acceptable starches, sugars, artificial sweetening agents, powdered celluloses, such as crystalline and microcrystalline celluloses, flours, gelatins, gums, etc.

Useful tablet formulations may be made by conventional compression, wet granulation or dry granulation methods and utilize pharmaceutically acceptable diluents, binding agents, lubricants, disintegrants, surface modifying agents (including surfactants), suspending or stabilizing agents, including, but not limited to, magnesium stearate, stearic acid, sodium lauryl sulfate, microcrystalline cellulose, methyl cellulose, sodium carboxymethyl cellulose, carboxymethylcellulose calcium, polyvinylpyrrolidine, gelatin, alginic acid, acacia gum, xanthan gum, sodium citrate, complex silicates, calcium carbonate, glycine, dextrin, sucrose, sorbitol, dicalcium phosphate, calcium sulfate, lactose, kaolin, mannitol, sodium chloride, talc, starches, sugars, low melting waxes, and ion exchange resins. Preferred surface modifying agents include nonionic and anionic surface modifying agents. Representative examples of surface modifying agents include, but are not limited to, poloxamer 188, benzalkonium. chloride, calcium stearate,

cetostearl alcohol, cetomacrogol emulsifying wax, sorbitan esters, colloidol silicon dioxide, phosphates, sodium dodecylsulfate, magnesium aluminium silicate, and triethanolamine. Oral formulations herein may utilize standard delay or time release formulations to alter the absorption of the active compound(s). The oral formulation may also consist of administering the active ingredient in water or a fruit juice, containing appropriate solubilizers or emulsifiers as needed.

Liquid carriers can be used in preparing solutions, suspensions, emulsions, syrups, and elixirs. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable oil or fat. The liquid carrier can obtain other suitable pharmaceutical additives such as, for example, solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavouring agents, suspending agents, thickening agents, colours, viscosity regulators, stabilizers or osmoregulators. Suitable examples of liquid carriers for oral and parenteral administration include water (particularly containing additives as above, e.g. cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols, e.g. glycols) and their derivatives, and oils (e.g. fractionated coconut oil and arachis oil).

For parenteral administration, the carrier can also be an oily ester such as ethyl oleate and isopropyl myristrate. Sterile liquid carriers are used in sterile liquid form compositions for parenteral administration. The liquid carrier for pressurized compositions can be halogenated hydrocarbon or other pharmaceutically acceptable propellant.

The compounds of this invention may also be administered parenterally or intraperitoneally. Solutions or suspensions of these active compounds as a free base or pharmacologically acceptable salt can be prepared in water suitably mixed with a surfactant such as hydroxy-propylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to inhibit the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

The carriers described above are not meant to be exclusive, but instead merely representative of the classes of carriers and the particular carriers that may be used in preferred dosage forms of the present invention.

A pharmaceutical product, as described herein, may include other pharmaceutically active substances. It can be prepared by mixing the active compounds with one or more pharmacologically tolerated carriers and converting the mixture into a suitable pharmaceutical form.

Use in clinical symptoms

Taking into account its 5-HT_{1A} receptor affinity and its neuroprotective capacity, the compounds of formula Ia are useful in the treatment and/or prophylaxis of pathological states wherein the 5-HT_{1A} receptor agonists are indicated, such as, for example, the treatment and/or prophylaxis of cerebral damage caused by thromboembolic stroke or traumatic brain damage, as well as the treatment and/or prevention of Parkinson's disease, depression, migraine, pain, psychosis such as e.g. schizophrenia; mood disorders, such as anxiety disorders (e.g. obsessive compulsive disorders, generalized anxiety) and aggressive disorders (including mixed aggressive-anxiety/depressive disorders); and urinary tract disorders, particularly urinary incontinence, in mammals, particularly in humans.

Additional objects, advantages and features of the invention will become apparent to those skilled in the art upon examination of the description or may be learned by practice of the invention. The following examples and drawings are provided by way of illustration, and is not intended to be limiting of the present invention.

EXAMPLES

Example 1. Synthesis of compounds of general structure Ia (n > 1). General procedure. (See scheme 1)

To a suspension of the bromoalkyl derivative **III** (4.5 mmol) and the appropriate arylpiperazine **IV** (7.5 mmol) in dry acetonitrile (10 mL) was added triethylamine (1.0 mL, 7.5 mmol), and the mixture was refluxed for 20-24 h. After cooling down, the solvent was evaporated under reduced pressure and the residue was resuspended in water and extracted with dichloromethane (3 x 50 mL). The combined organic layers were washed with water and dried over anhydrous Na_2SO_4. After evaporation of the solvent the crude oil was purified by column chromatography in silica gel using the appropriate eluent. Collected data of IR and NMR spectra refer to free bases, then hydrochloride salts were prepared prior to mp, elemental analyses and biological assays.

Example 2. 2-[4-[4-(Naphth-1-yl)piperazin-1-yl]butyl]-1,4-dioxoperhydropyrrolo[1,2-*a*]pyrazine **(g)**.

The title compound was prepared following general procedure described in example 1, starting from 2-(4-bromobutyl)-1,4-dioxoperhydropyrrolo[1,2-*a*]pyrazine and 1-(naphth-1-yl)piperazine as reagents,

Chromatography: chloroform/methanol, from 9.5:0.5 to 9:1.
Yield: 43%; mp: 277-280 °C (d) (methanol/ethyl ether).

IR ($CHCl_3$): 1670, 1600, 1580, 1460 cm^{-1}.

^1H NMR ($CDCl_3$): δ 1.56-1.65 (m, 4H), 1.88-2.12 (m, 3H), 2.35-2.41 (m, 1H), 2.51 (t, *J* = 6.9, 2H), 2.74 (br s, 4H), 3.15 (br s, 4H), 3.33-3.41 (m, 1H), 3.50-3.63 (m, 3H), 3.79 (d, *J* = 16.2, 1H), 4.07 (t, *J* = 7.8, 1H), 4.14 (d, *J* = 16.2, 1H), 7.09 (dd, *J* = 7.3, 1.0, 1H), 7.39 (t, *J* = 7.8, 1H), 7.44-7.48 (m, 2H), 7.55 (d, *J* = 8.4, 1H), 7.80-7.83 (m, 1H), 8.17-8.20 (m, 1H).

^{13}C NMR ($CDCl_3$): δ 22.6, 23.8, 25.0, 28.8, 45.2, 45.9, 51.6, 52.7, 53.6, 58.0, 59.0, 114.6, 123.4 (2 C), 125.2, 125.7, 125.8, 128.3, 128.7, 134.6, 149.4, 163.1, 167.1.

Anal. calculated for $C_{25}H_{32}N_4O_2 \cdot HCl \cdot 1/2H_2O$: C, 64.43, H, 7.35, N, 12.02; found: C, 64.57, H, 7.20, N, 11.89.

Example 3. (2*R*,8a*RS*)-2-[4-[4-(Naphth-1-yl)-2-methylpiperazin-1-yl]butyl]-1,4-dioxoperhydropyrrolo[1,2-*a*]pyrazine, **(a)** (mixture of diastereoisomers).

The title compound was prepared following general procedure described in example 1, starting from 2-(4-bromobutyl)-1,4-dioxoperhydropyrrolo[1,2-*a*]pyrazine and (*R*)-3-methyl-1-(naphth-1-yl)piperazine as reagents,

Chromatography: chloroform/ethanol, from 20:1 to 12:1.
Yield: 57% (oil); $[\alpha]_D^{25}$ = –20.0 (c = 1.1, $CHCl_3$).

IR ($CHCl_3$): 1665, 1575, 1510, 1460 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ 1.16 (d, *J* = 5.6, 3H), 1.50-1.60 (m, 4H), 1.80-2.14 (m, 3H), 2.30-2.45 (m, 2H), 2.59-2.89 (m, 4H), 3.03-3.08 (m, 2H), 3.18-3.23 (m, 2H), 3.28-3.67 (m, 4H), 3.77 (dd, *J* = 16.4, 2.2, 1H), 4.03 (t, *J* = 7.6, 1H), 4.14 (d, *J* = 16.4, 1H), 7.05 (dd, *J* = 7.6, 1.2, 1H), 7.36 (t, *J* = 8.1, 1H), 7.38-7.46 (m, 2H), 7.51 (d, *J* = 8.4, 1H), 7.74-7.81 (m, 1H), 8.13-8.18 (m, 1H).

^{13}C NMR ($CDCl_3$): δ 22.6 (2 C), 23.1, 25.1, 28.8, 29.6, 45.2, 45.9 (2 C), 51.6 (2 C), 53.0, 55.4, 59.0, 60.1, 114.6, 123.4 (2 C), 125.2, 125.7, 125.8, 128.3, 128.8, 134.6, 149,3, 163.1, 167.1.

Example 4. (2*S*,8a*RS*)-2-[4-[4-(Naphth-1-yl)-2-methylpiperazin-1-yl]butyl]-1,4-dioxoperhydropyrrolo[1,2-*a*]pyrazine, **(b)** (mixture of diastereoisomers).

The title compound was prepared following general procedure described in example 1, starting from 2-(4-bromobutyl)-1,4-dioxoperhydropyrrolo[1,2-*a*]pyrazine and (*S*)-3-methyl-1-(naphth-1-yl)piperazine as reagents,

Chromatography: chloroform/ethanol, from 20:1 to 12:1.
Yield: 35% (oil). $[\alpha]_D^{25}$ +21.0 (c = 1.1, $CHCl_3$).

Spectral data are identical to those of **3** (see above).

Example 5. 2-[4-[4-(3,4-Dihydro-2*H*-1,5-benzodioxepin-6-yl)piperazin-1-yl]butyl]-1,4-dioxoperhydropyrrolo[1,2-*a*]pyrazine, **(h).**

The title compound was prepared following general procedure described in example 1, starting from 2-(4-bromobutyl)-1,4-dioxoperhydropyrrolo[1,2-*a*]pyrazine and 1-(3,4-dihydro-2*H*-1,5-benzodioxepin-6-yl)piperazine as reagents,

Chromatography: chloroform/methanol, from 9.5:0.5 to 9:1.
Yield 52%. mp 212-213 °C (d) (methanol/ethyl ether).

IR ($CHCl_3$): 1670, 1590, 1485, 1460 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ 1.43-1.55 (m, 4H), 1.82-2.05 (m, 3H), 2.13 (qt, *J* = 5.7, 2H), 2.27-2.31 (m, 1H), 2.35 (t, *J* = 7.2, 2H), 2.55 (br s, 4H), 3.00 (br s, 4H), 3.27-3.34 (m, 1H), 3.41-3.57 (m, 3H), 3.72 (d, *J* = 16.2, 1H), 4.01 (t, *J* = 7.5, 1H), 4.07 (d, *J* = 16.5, 1H), 4.14-4.21 (m, 4H), 6.54 (dd, *J* = 7.8, 1.5, 1H), 6.59 (dd, *J* = 8.2, 1.4, 1H), 6.76 (t, *J* = 7.9, 1H).

^{13}C NMR ($CDCl_3$): δ 22.6, 23.9, 25.1, 28.8, 31.5, 45.2, 46.0, 51.0, 51.6, 53.4, 58.0, 59.0, 70.2, 70.3, 112.9, 115.5, 122.5, 144.6, 145.0, 152.1, 163.1, 167.1.

Anal. calculated for $C_{24}H_{34}N_4O_4.2HCl.2H_2O$: C, 52.26, H, 7.31, N, 10.15; found: C, 52.02, H, 6.93, N, 10.07.

Example 6. Synthesis of compounds of general structure Ia (n = 1). General procedure. (See scheme 1)

To a suspension of intermediate **II** (7 mmol) and formaldehyde (7 mmol from a 35% aqueous solution) in methanol (15 mL) was added the corresponding arylpiperazine **IV** (7 mmol). The resultant suspension was

refluxed for 2-6 hours after complete disappearance of the starting materials (TLC). The mixture was then cooled to room temperature, and the solvent was evaporated at reduced pressure. The crude mixture was diluted in chloroform (75 mL) and washed with water (3 x 75 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated at reduced pressure. The obtained crude was purified by column chromatography on silica gel using the appropriate eluent. Collected data of IR and NMR spectra refer to free bases, then hydrochloride salts were prepared prior to mp, elemental analyses and biological assays.

Example 7. (2*R*,8a*R*)-2-[[4-(Naphth-1-yl)-2-methylpiperazin-1-yl]methyl]-1,4-dioxoperhydropyrrolo[1,2-*a*]pyrazine, **(c)**

The title compound was prepared following general procedure described in example 6, starting from (*R*)-1,4-dioxoperhydropyrrolo[1,2-*a*]pyrazine and (*R*)-3-methyl-1-(naphth-1-yl)piperazine as reagents,

Chromatography: from ethyl acetate to ethyl acetate/ethanol, 9:1.
Yield: 23%. $[\alpha]_D^{25}$ =+36.6 (*c* = 1.9, $CHCl_3$).

IR ($CHCl_3$): 1665, 1595, 1575, 1500, 1455 cm^{-1}.

^1H NMR ($CDCl_3$): δ 1.22 (d, *J* = 7.2, 3H), 1.80-1.94 (m, 1H), 1.96-2.16 (m, 2H), 2.32-2.42 (m, 2H), 2.72-2.79 (m, 2H), 2.88-3.02 (m, 2H), 3.14-3.28 (m, 2H), 3.49-3.69 (m, 2H), 4.00-4.15 (m, 3H), 4.25 (d, *J* = 12.3, 1H), 4.40 (d, *J* = 12.3, 1H), 7.02 (dd, *J* = 7.5, 0.9, 1H), 7.37 (t, *J* = 7.5, 1H), 7.42-7.46 (m, 2H), 7.52 (d, *J* = 8.1, 1H), 7.78-7.81 (m, 1H), 8.15-8.19 (m, 1H).

^{13}C NMR ($CDCl_3$): δ 22.7 (2 C), 28.6, 45.1, 45.2, 51.0, 52.9, 53.5, 59.1, 60.3, 63.7, 114.6, 123.3, 123.5, 125.3, 125.7 (2 C), 128.3, 128.7, 134.6, 149.2, 163.8, 168.1.

Anal. calculated for $C_{23}H_{28}N_4O_2.HCl.5/2H_2O$: C, 58.27, H, 7.23, N, 11.82; found: C, 58.25, H, 6.80, N, 11.50.

Example 8. (2*S*,8a*S*)-2-[[4-(Naphth-1-yl)-2-methylpiperazin-1-yl]methyl]-1,4-dioxoperhydropyrrolo[1,2-*a*]pyrazine, **(d)**

The title compound was prepared following general procedure described in example 6, starting from (*S*)-1,4-dioxoperhydropyrrolo[1,2-*a*]pyrazine and (*S*)-3-methyl-1-(naphth-1-yl)piperazine as reagents,

Yield: 36%. $[\alpha]_D^{25}$ =–38.0 (*c* = 1.2, $CHCl_3$).

Spectral data are identical to those of **(c)** (see above).

Anal. calculated for $C_{23}H_{28}N_4O_2.HCl.2/3H_2O$: C, 62.64, H, 6.88, N, 12.71; found: C, 62.51, H, 7.04, N, 12.97.

Example 9. (2*R*,8a*S*)-2-[[4-(Naphth-1-yl)-2-methylpiperazin-1-yl]methyl]-1,4-dioxoperhydropyrrolo[1,2-*a*]pyrazine, **(e)**

The title compound was prepared following general procedure described in example 6, starting from (*S*)-1,4-dioxoperhydropyrrolo[1,2-*a*]pyrazine and (*R*)-3-methyl-1-(naphth-1-yl)piperazine as reagents,

Chromatography: from ethyl acetate to ethyl acetate/ethanol, 9:1.
Yield: 43%. $[\alpha]_D^{25}$ =–53.2 (*c* = 1.4, $CHCl_3$).

IR ($CHCl_3$): 1665, 1595, 1575, 1500, 1455 cm^{-1}.

^1H NMR ($CDCl_3$): δ 1.22 (m, 3H), 1.85-1.94 (m, 1H), 1.96-2.17 (m, 2H), 2.34-2.42 (m, 2H), 2.62-2.80 (m, 2H), 2.85-3.04 (m, 2H); 3.14-3.24 (m, 2H), 3.51-3.68 (m, 2H), 4.05-4.18 (m, 3H), 4.28-4.38 (m, 2H), 7.03 (d, *J* = 7.2, 1H), 7.37 (t, *J* = 7.8, 1H), 7.43-7.46 (m, 2H), 7.52 (d, *J* = 8.1, 1H), 7.78-7.81 (m, 1H), 8.15-8.18 (m, 1H).

^{13}C NMR ($CDCl_3$): δ 22.6 (2 C), 28.7, 45.1 (2 C), 50.6, 53.0, 53.4, 59.1, 60.3, 63.2, 114.6, 123.3, 123.5, 125.3, 125.8 (2 C), 128.3, 128.7, 134.6, 149.2, 163.6, 168.0.

Anal. calculated for $C_{23}H_{28}N_4O_2.HCl.H_2O$: C, 61.80, H, 6.99, N, 12.54; found: C, 61.47, H, 7.06, N, 12.54.

Example 10. (2*S*,8a*R*)-2-[[4-(Naphth-1-yl)-2-methylpiperazin-1-yl]methyl]-1,4-dioxoperhydropyrrolo[1,2-*a*]pyrazine, **(f)**

The title compound was prepared following general procedure described in example 6, starting from (*R*)-1,4-dioxoperhydropyrrolo[1,2-*a*]pyrazine and (*S*)-3-methyl-1-(naphth-1-yl)piperazine as reagents,

Yield: 40%. $[\alpha]_D^{25}$ =+53.7 (*c* = 0.9, $CHCl_3$).

Spectral data are identical to those of **(e)** (see above).

Anal. calculated for $C_{23}H_{28}N_4O_2.HCl.3/2H_2O$: C, 60.58, H, 7.07, N, 12.29; found: C, 60.72, H, 7.13, N, 12.04.

Example 11. (2*R*,7a*RS*)-(-)-2-[3-[4-(3-Chlorophenyl)-2-methylpiperazin-1-yl]propyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole, **(i)** (mixture of diasteroisomers)

The title compound was prepared following general procedure described in example 1, starting from 2-(3-bromopropyl)-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole and (*R*)-1-(3-chlorophenyl)-3-methylpiperazine as reagents,

Chromatography: dichloromethane/ethanol, from 9.8:0.2 to 9.5:0.5.
Yield: 51%; $[\alpha]_D^{25}$ = -31.1 (c = 1.1, $CHCl_3$).

IR ($CHCl_3$): 1770, 1710, 1543, 1447, 1420 cm^{-1}.

^1H NMR ($CDCl_3$): δ 1.09 (d, *J* = 5.7, 3H), 1.58-1.84 (m, 3H), 1.93-2.04 (m, 2H), 2.08-2.38 (m, 3H), 2.48-2.97 (m, 5H), 3.12-3.25 (m, 1H), 3.30-3.68 (m, 5H), 4.01 (dd, *J* = 8.9, 7.4, 1H), 6.67-6.79 (m, 3H), 7.09 (t, *J* = 8.1, 1H).

^{13}C NMR ($CDCl_3$): δ 15.9, 24.4, 27.0, 27.6, 37.4, 45.6, 48.6, 50.3, 50.7, 55.0, 55.7, 63.5, 113.9, 115.8, 119.2, 130.0, 135.0, 152.2, 160.8, 174.0.

Example 12. (2*S*,7a*RS*)-(+)-2-[3-[4-(3-Methoxyphenyl)-2-methylpiperazin-1-yl]propyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole, **(j)** (mixture of diasteroisomers)

The title compound was prepared following general procedure described in example 1, starting from 2-(3-bromopropyl)-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole and (*S*)-1-(3-methoxyphenyl)-3-methylpiperazine as reagents,

Chromatography: from dichloromethane to dichloromethane/ethanol 9.5:0.5.
Yield: 77%; $[\alpha]_D^{25}$ = +0.7 (c = 1.0, $CHCl_3$).

IR ($CHCl_3$): 1770, 1710, 1497, 1447, 1420 cm^{-1}.

^1H NMR ($CDCl_3$): δ 1.13 (d, *J* = 5.7, 3H), 1.58-1.91 (m, 3H), 1.98-2.14(m, 2H), 2.17-2.46 (m, 3H), 2.50-2.99 (m, 5H), 3.18-3.30 (m, 1H), 3.35-3.74 (m, 5H), 3.78 (s, 3H), 4.07 (dd, *J* = 9.0, 7.4, 1H), 6.37-6.53 (m, 3H), 7.15 (t, *J* = 8.0, 1H).

^{13}C NMR ($CDCl_3$): δ 18.6, 24.5, 27.2, 27.7, 37.6, 45.7, 49.1, 50.7, 50.9, 55.3, 55.4, 58.6, 63.5, 102.6, 104.6, 109.0, 129.9, 152.6, 160.8 (2C), 174.1.

Example 13. (2*S*,7a*RS*)-(-)-2-[3-[4-(1-Benzofuran-7-yl)-2-methylpiperazin-1-yl]propyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole, **(k)** (mixture of diasteroisomers)

The title compound was prepared following general procedure described in example 1, starting from 2-(3-bromopropyl)-1,3-dioxoperhydropyrrolo[1,2-c]imidazole and (S)-1-(1-benzofuran-7-yl)-3-methylpiperazine as reagents,

Chromatography: dichloromethane/ethanol, 9:1.
Yield: 74%; $[\alpha]_D^{25}$ = -1.5 (c = 1.8, $CHCl_3$).

IR ($CHCl_3$): 1770, 1710, 1589, 1447, 1420 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ 1.07 (d, J = 5.2, 3H), 1.50-1.65 (m, 1H), 1.77 (qt, J = 7.2, 2H), 1.87-2.04 (m, 2H), 2.10-2.35 (m, 2H), 2.41-2.52 (m, 1H), 2.62-2.85 (m, 3H), 2.92-3.03 (m, 2H), 3.10-3.22 (m, 1H), 3.42-3.67 (m, 5H), 3.99 (t ap, J = 8.1, 1H), 6.65-6.69 (m, 2H), 7.02-7.15 (m, 2H), 7.52 (d, J = 1.5, 1H).

^{13}C NMR ($CDCl_3$): δ 16.0, 24.3, 26.8, 27.4, 37.4, 45.4, 49.8, 50.6, 50.7, 54.9, 56.8, 63.2, 106.8, 110.9, 113.9, 123.4, 128.4, 137.3, 143.8, 146.7, 160.7, 173.8.

Example 14. (2R,7aRS)-(-)-2-[4-[2-Ethyl-4-(naphth-1-yl)piperazin-1-yl]butyl]-1,3-dioxoperhydropyrrolo[1,2-c]imidazole, **(l)** (mixture of diasteroisomers)

The title compound was prepared following general procedure described in example 1, starting from 2-(4-bromobutyl)-1,3-dioxoperhydropyrrolo[1,2-c]imidazole and (R)-3-ethyl-1-(naphth-1-yl)piperazine as reagents,

Chromatography: dichloromethane/ethanol, 9.8:0.2.
Yield: 75%; $[\alpha]_D^{25}$ = -11.5 (c = 1.9, $CHCl_3$).

IR ($CHCl_3$): 1770, 1717, 1651, 1558, 1458, 1420 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ 0.87 (t, J = 7.5, 3H), 1.55-1.74 (m, 7H), 1.94-2.24 (m, 3H), 2.41-2.95 (m, 5H), 2-99-3.31 (m, 5H), 3.47 (t, J = 6.8, 2H), 3.63 (dt, J = 11.2, 7.8, 1H), 4.03 (dd, J = 8.9, 7.5, 1H), 7.04 (d, J = 7.4, 1H), 7.29-7.52 (m, 4H), 7.74-7.78 (m, 1H), 8.08-8.13 (m, 1H).

^{13}C NMR ($CDCl_3$): δ 10.5, 23.3, 26.3, 27.1, 27.7, 38.9, 45.7, 50,5, 52.9, 53.0, 56.9, 61.4, 63.5, 114.8, 123.6, 123.7, 125.4, 125.9, 126.0, 128.5, 129.1, 134.9, 149.9, 161.0, 174.1.

Example 15. (2*R*,7a*RS*)-(-)-2-[4-[4-(Benzimidazol-4-yl)-2-methylpiperazin-1-yl]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole, **(m)** (mixture of diasteroisomers) ugl Ex 20

The title compound was prepared following general procedure described in example 1, starting from 2-(4-bromobutyl)-1,3-

dioxoperhydropyrrolo[1,2-c]imidazole and (R)-4-(3-methylpiperazin-1-yl)benzimidazole as reagents,

Chromatography: dichloromethane/methanol, 9:1.
Yield: 73%; $[\alpha]_D^{25}$ = -41.3 (c = 1.2, $CHCl_3$).

IR ($CHCl_3$): 1770, 1705, 1508, 1447, 1420 cm^{-1}.

^1H NMR ($CDCl_3$): δ 1.07-1.12 (m, 3H), 1.52-1.71 (m, 5H), 1.96-2.36 (m, 6H), 2.51-2.73 (m, 4H), 2.93-3.24 (m, 3H), 3.44 (t, *J* = 7.1, 2H), 3.61 (dt, *J* = 11.2, 7.6, 1H), 4.02 (dd, *J* = 9.0, 7.4, 1H), 6.58-6.62 (m, 1H), 7.09-7.12 (m, 2H), 7.92 (s, 1H).

^{13}C NMR ($CDCl_3$): δ 16.7, 22.7, 26.3, 27.1, 27.7, 38.9, 45.6, 50.6, 51.3, 53.0, 55.1, 57.6, 63.5, 108.7, 123.8, 138.0, 161.0, 174.2.

Example 16. (2*S*,7a*RS*)-(+)-2-[4-[4-(1-Benzofuran-7-yl)-2-methylpiperazin-1-yl]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole **(n)** (mixture of diasteroisomers),

The title compound was prepared following general procedure described in example 1, starting from 2-(4-bromobutyl)-1,3-dioxoperhydropyrrolo[1,2-c]imidazole and (S)-1-(1-benzofuran-7-yl)-3-methylpiperazine as reagents,

Chromatography: dichloromethane/ethanol, 9.5:0.5.
Yield: 76%; $[\alpha]_D^{25}$ = +16.7 (c = 1.1, $CHCl_3$).

IR ($CHCl_3$): 1770, 1705, 1651, 1458, 1420 cm^{-1}.

^1H NMR ($CDCl_3$): δ 1.08 (d, *J* = 5.7, 3H), 1.45-1.65 (m, 5H), 1.90-2.06 (m, 2H), 2.10-2.37 (m, 2H), 2.44-2.82 (m, 4H), 2.91-3.02 (m, 2H), 3.13-3.22 (m, 1H), 3.44 (t, *J* = 7.1, 2H), 3.51-3.63 (m, 3H), 3.99 (dd, *J* = 9.0, 7.5, 1H), 6.65-6.69 (m, 2H), 7.02-7.15 (m, 2H), 7.52 (d, *J* = 2.2, 1H).

^{13}C NMR ($CDCl_3$): δ 16.3, 22.9, 26.1, 26.9, 27.5, 38.7, 45.5, 49.9, 51.0, 52.9, 54.9, 56.9, 63.3, 106.8, 111.1, 114.0, 123.5, 128.5, 137.4, 143.9, 146.8, 160.8, 173.9.

Example 17. (2*R*,7a*RS*)-(-)-2-[4-[2-Ethyl-4-(3-methoxyphenyl)piperazin-1-yl]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole, **(o)** (mixture of diasteroisomers)

The title compound was prepared following general procedure described in example 1, starting from 2-(4-bromobutyl)-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole and (*R*)-3-ethyl-1-(3-methoxyphenyl)piperazine as reagents,

Chromatography: dichloromethane/ethanol, 9.5:0.5.
Yield: 49%; $[\alpha]_D^{25}$ = –23.3 (c = 1.2, $CHCl_3$).

IR ($CHCl_3$): 1770, 1705, 1539, 1447, 1420 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ 0.87 (t, *J* = 7.5, 3H), 1.40-1.66 (m, 7H), 1.96-2.07 (m, 2H), 2.15-2.39 (m, 4H), 2.66-2.76 (m, 2H), 2.85-2.90 (m, 2H), 3.14-3.35 (m, 3H), 3.43 (t, *J* = 7.0, 2H), 3.61 (dt, *J* = 12.0, 8.0, 1H), 3.72 (s, 3H), 4.01 (dd, *J* = 9.1, 7.4, 1H), 6.31-6.49 (m, 3H), 7.09 (t, *J* = 8.1, 1H).

^{13}C NMR ($CDCl_3$): δ 10.4, 23.0, 26.1, 27.0, 27.6, 38.8, 45.6, 48.6, 50.5, 52.5, 52.7, 55.2, 60.6, 63.4, 102.6, 104.4, 109.0, 129.8, 152.8, 160.6, 160.8, 174.0.

Example 18. (2*S*,7a*RS*)-(+)-2-[4-[2-Methyl-4-(4-methylnaphth-1-yl)piperazin-1-yl]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole, **(p)** (mixture of diasteroisomers)

The title compound was prepared following general procedure described in example 1, starting from 2-(4-bromobutyl)-1,3-dioxoperhydropyrrolo[1,2-c]imidazole and (S)-3-methyl-1-(4-methylnaphth-1-yl)piperazine as reagents,

Chromatography: dichloromethane/ethanol, 9.5:0.5.
Yield: 65%; $[\alpha]_D^{25}$ = +19.3 (c = 1.5, $CHCl_3$).

IR ($CHCl_3$): 1770, 1705, 1543, 1447, 1420 cm^{-1}.

^1H NMR ($CDCl_3$): δ 1.08-1.14 (m, 3H), 1.58-1.73 (m, 5H), 1.97-2.48 (m, 6H), 2.56 (s, 3H), 2.69-3.25 (m, 7H), 3.46 (t, *J* = 6.9, 2H), 3.63 (dt, *J* = 11.2, 7.6, 1H), 4.03 (dd, *J* = 9.0, 7.4, 1H), 6.94 (d, *J* = 7.5, 1H), 7.17 (d, *J* = 8.9, 1H), 7.38-7.48 (m, 2H), 7.87-7.92 (m, 1H), 8.16-8.21 (m, 1H).

^{13}C NMR ($CDCl_3$): δ 19.3 (2C), 23.3, 26.4, 27.2, 27.7, 39.0, 45.7, 51.8, 53.2, 53.5, 55.5, 60.6, 63.5, 114.7, 124.2, 124.8, 125.2, 125.8, 126.6, 129.2, 129.6, 133.8, 148.3, 161.0, 174.2.

Example 19. (2*S*,7a*RS*)-(+)-2-[4-[2-Methyl-4-phenylpiperazin-1-yl]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole, **(q)** (mixture of diasteroisomers)

The title compound was prepared following general procedure described in example 1, starting from 2-(4-bromobutyl)-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole and (*S*)-3-methyl-1-phenylpiperazine as reagents,

Chromatography: dichloromethane/ethanol, 9.5:0.5.
Yield: 75%; $[\alpha]_D^{25}$ = +19.3 (c = 1.5, $CHCl_3$).

IR ($CHCl_3$): 1770, 1710, 1497, 1447, 1420 cm^{-1}.

^1H NMR ($CDCl_3$): δ 1.05 (d, *J* = 5.8, 3H), 1.35-1.70 (m, 5H), 1.88-2.16 (m, 2H), 2.18-2.41 (m, 4H), 2.48-2.92 (m, 4H), 3.13-3.23 (m, 1H), 3.30-3.46 (m, 4H), 3.60 (dt, *J* = 11.2, 7.6, 1H), 4.00 (dd, *J* = 9.0, 7.5, 1H), 6.73-6.86 (m, 3H), 7.14-7.22 (m, 2H).

^{13}C NMR ($CDCl_3$): δ 16.6, 23.2, 26.3, 27.2, 27.7, 39.0, 45.7, 49.4, 51.1, 53.0, 55.1, 56.4, 63.5, 116.2, 119.7, 129.2, 151.4, 161.0, 174.1.

ugl Ex 15

Example 20. (2*S*,7a*RS*)-(+)-2-[4-[4-(Benzimidazol-4-yl)-2-methylpiperazin-1-yl]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole, **(r)** (mixture of diasteroisomers)

The title compound was prepared following general procedure described in example 1, starting from 2-(4-bromobutyl)-1,3-dioxoperhydropyrrolo[1,2-c]imidazole and (S)-4-(3-methylpiperazin-1-yl)benzimidazole as reagents,

Chromatography: dichloromethane/ethanol, 9.5:0.5.
Yield: 33%; $[\alpha]_D^{25}$ = +12.3 (c = 1.6, $CHCl_3$).

Spectral data are identical to those of 5) (see above).

Example 21. (2*S*,7a*RS*)-(+)-2-[4-[2-Methyl-4-(4-nitronaphth-1-yl)piperazin-1-yl]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole, **(s)** (mixture of diasteroisomers)

The title compound was prepared following general procedure described in example 1, starting from 2-(4-bromobutyl)-1,3-dioxoperhydropyrrolo[1,2-c]imidazole and (S)-3-methyl-1-(4-nitronaphth-1-yl)piperazine as reagents,

Chromatography: dichloromethane/ethanol, from 9.8:0.2 to 9:1.
Yield: 85%; $[\alpha]_D^{25}$ = +39.4 (c = 1.1, $CHCl_3$).

IR ($CHCl_3$): 1770, 1705, 1508, 1446, 1416, 1261, 1215 cm^{-1}.

^1H NMR ($CDCl_3$): δ 1.17 (d, *J* = 6.1, 3H), 1.54-1.73 (m, 5H), 2.02-2.49 (m, 4H), 2.63-3.38 (m, 9H), 3.53 (t, *J* = 7.0, 2H), 3.68 (dt, *J* = 11.2, 7.7, 1H), 4.10 (dd, *J* = 9.0, 7.6, 1H), 6.99 (d, *J* = 6.0, 1H), 7.54-7.71 (m, 2H), 8.21 (d, *J* = 6.0, 1H), 8.29 (d, *J* = 9.0, 1H), 8.72 (d, *J* = 9.0, 1H).

^{13}C NMR ($CDCl_3$): δ 19.5, 23.4, 26.5, 27.4, 28.0, 39.1, 45.9, 51.8, 53.2, 55.4, 60.2, 63.8, 112.5, 124.2, 125.0, 126.5, 126.7, 127.6, 128.7, 129.8, 141.4, 156.3, 161.2, 174.4.

Example 22. Radioligand Binding Assays.

For all receptor binding assays, male Sprague-Dawley rats (*Rattus norvegicus albinus*), weighing 180-200 g, were killed by decapitation and the

brains rapidly removed and dissected. Tissues were stored at -80 °C for subsequent use and homogenized on a Polytron PT-10 homogenizer. Membrane suspensions were centrifuged on a Beckman J2-HS instrument.

5-HT_{1A} Receptor.

The cerebral cortex was homogenized in 10 volumes of ice-cold Tris buffer (50 mM Tris-HCl, pH 7.7 at 25 °C) and centrifuged at 28000*g* for 15 min. The membrane pellet was washed twice by resuspension and centrifugation. After the second wash the resuspended pellet was incubated at 37 °C for 10 min. Membranes were then collected by centrifugation and the final pellet was resuspended in 50 mM Tris-HCl, 5 mM $MgSO_4$, and 0.5 mM EDTA buffer (pH 7.4 at 37 °C). Fractions of 100 µL of the final membrane suspension (about 1 mg of protein) were incubated at 37 °C for 15 min with 0.6 nM [^{3}H]-8-OH-DPAT (133 Ci/mmol), in the presence or absence of the competing drug, in a final volume of 1.1 mL of assay buffer (50 mM Tris-HCl, 10 nM clonidine, 30 nM prazosin, pH 7.4 at 37 °C). Nonspecific binding was determined with 10 µM 5-HT.

α_1 Adrenoceptor.

The cerebral cortex was homogenized in 20 volumes of ice-cold buffer (50 mM Tris-HCl, 10 mM $MgCl_2$, pH 7.4 at 25 °C) and centrifuged at 30000*g* for 15 min. Pellets were washed twice by resuspension and centrifugation. Final pellets were resuspended in the same buffer. Fractions of the final membrane suspension (about 250 µg of protein) were incubated at 25 °C for 30 min with 0.2 nM [^{3}H]prazosin (23 Ci/mmol), in the presence or absence of six concentrations of the competing drug, in a final volume of 2 mL of buffer. Nonspecific binding was determined with 10 µM phentolamine.

For all binding assays, competing drug, nonspecific, total and radioligand bindings were defined in triplicate. Incubation was terminated by rapid vacuum filtration through Whatman GF/B filters, presoaked in 0.05% poly(ethylenimine), using a Brandel cell harvester. The filters were then washed with the assay buffer, dried and placed in poly(ethylene) vials to which were added 4 mL of a scintillation cocktail (Aquasol). The radioactivity bound to the filters was measured by liquid scintillation spectrometry. The

data were analyzed by an iterative curve-fitting procedure (program Prism, Graph Pad), which provided IC_{50}, K_i, and r^2 values for test compounds, K_i values being calculated from the Cheng and Prusoff equation. The protein concentrations of the rat cerebral cortex and the rat striatum were determined by the method of Lowry, using bovine serum albumin as the standard.

Results from these assays are presented below in Table 1.

Table 1. Binding data of compounds Ia

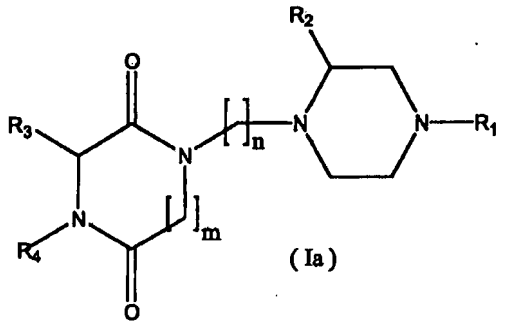
Compound	$K_i \pm$ SEM ($5\text{-}HT_{1A}$)	$K_i \pm$ SEM (α_1)
(g)	0.5 ± 0.2	8.0 ± 1.7
(a)	4.2 ± 0.9	20.1 ± 0.8
(b)	15.3 ± 1.8	34.4 ± 1.2
(h)	3.1 ± 0.9	348 ± 21
(c)	9.5 ± 2.2	>1000
(d)	2.5 ± 0.1	>1000
(e)	6.3 ± 0.2	>1000
(f)	6.4 ± 0.1	>1000
(i)	11.7 ± 3.4	76%*
(j)	21.9 ± 5.1	56%*
(k)	6.7 ± 0.5	64%*
(l)	2.4 ± 0.3	87%*
(m)	2.3 ± 0.3	>1000
(n)	1.6 ± 0.4	75%*
(o)	21.0 ± 3.0	64%*
(p)	15.3 ± 0.8	75%*
(q)	22.1 ± 0.1	62%*
(r)	4.1 ± 0.3	>1000
(s)	87%*	66%*

Values are means of 2-4 experiments performed in triplicate.

* % of displacement at 10^{-6} M

CLAIMS

1. A compound of formula Ia:



(Ia)

wherein:
m is an integer from 0 to 1;
R_3 and R_4 are H or are methylene groups bound together forming with the heterocyclic ring a 5- or 6- membered ring;
n is an integer from 1 to 4;
R_1 is selected from naphth-1-yl; naphth-2-yl; benzodioxepin-6-yl, benzodioxan-4-yl, benzimidazol-4-yl, dihydro-2*H*-1,5-benzodioxan-5-yl, 7-benzofuranyl, tetrahydronaphthyl or phenyl, wherein phenyl, tetrahydronaphthyl and naphtyl are each optionally substituted with one or more groups chosen from (C_1-C_6)-alkoxy, (C_1-C_6)alkyl, halogen, (C_2-C_6)-alkenyl, halo-(C_1-C_6)-alkyl, phenyl, phenyl(C_1-C_6)-alkyl, phenoxy, (C_1-C_6)-alkylcarbonyl, phenylcarbonyl, phenyl(C_1-C_6)alkylcarbonyl, (C_1-C_6)-alkoxycarbonyl, phenyl(C_1-C_6)alkoxycarbonyl, (C_1-C_6)-alkylcarbonylamino, hydroxy, cyano, nitro, amino, carboxy, sulfo, sulfamoyl, sulfonylamino, (C_1-C_6)alkylaminosulfonyl or (C_1-C_6)alkylsulfonylamino; and
R_2 is selected from (C_1-C_4)alkyl, (C_2-C_4)alkenyl, (C_1-C_4)alkoxy, halo-(C_1-C_4)alkyl, halogen, hydroxyl, amino, cyano;
their stereoisomers, N-oxides, crystalline forms, hydrates, pharmaceutically acceptable salts and pharmaceutically acceptable solvates.

2. The compound according to claim 1, wherein R_3 and R_4 are methylene groups bound together forming with the heterocyclic ring a 5- membered ring.

3. The compound according to any one of claims 1 to 2, wherein R_1 is selected from naphth-1-yl, benzimidazol-4-yl, 7-benzofuranyl, benzodioxepin-6-yl, or phenyl, wherein phenyl, and naphtyl are each optionally substituted with one or more groups chosen from (C_1-C_6)alkoxy, (C_1-C_6)alkyl, nitro, or halogen.

4. The compound according to any one of claims 1 to 3 wherein R_2 = (C_1-C_4)alkyl.

5. The compound according to claim 4, wherein R_3 and R_4 are methylene groups bound together forming with the heterocyclic ring a 5- membered ring, R_2=(C_1-C_4)alkyl, and R_1 is selected from naphth-1-yl, benzimidazol-4-yl, 7-benzofuranyl, benzodioxepin-6-yl, or phenyl, wherein phenyl, and naphtyl are each optionally substituted with one or more groups chosen from (C_1-C_6)alkoxy, (C_1-C_6)alkyl, nitro, or halogen.

6. The compound according to any one of claims 1 to 5, wherein R_1 is selected from unsubstituted naphth-1-yl, benzimidazol-4-yl and benzodioxepin-6-yl.

7. The compound according to any of claims 1 to 6 wherein:
R_3 and R_4 are methylene groups bound together forming with the heterocyclic ring a 5- membered ring;
m = 1;
n = 1;
R_1 is naphth-1-yl; and
R_2 = (C_1-C_4)alkyl.

8. The compound according to any of claims 1 to 6 wherein:
R_3 and R_4 are methylene groups bound together forming with the heterocyclic ring a 5- membered ring;
m = 1;
n = 4;
R_1 is naphth-1-yl; and
R_2 = (C_1-C_4)alkyl.

9. The compound according to any one of claims 1 to 5, wherein R_1 is

selected from 3-chlorophenyl, 3-methoxyphenyl, 4-methylnaphth-1-yl, 1-benzofuran-7-yl, naphtha-1-yl, benzimidazole-4-yl, 4-nitronapth-1-yl, and phenyl.

10. The compound according to claim 9, wherein:
R_3 and R_4 are methylene groups bound together forming with the heterocyclic ring a 5- membered ring;
m = 0;
n = 3;
R_1 is selected from 3-chlorophenyl, 3-methoxyphenyl, and 1-benzofuran-7-yl; and
R_2 = (C_1-C_4)alkyl.

11. The compound according to claim 9, wherein:
R_3 and R_4 are methylene groups bound together forming with the heterocyclic ring a 5- membered ring;
m = 0;
n = 4;
R_1 is selected from 3-methoxyphenyl, 4-methylnaphth-1-yl, 1-benzofuran-7-yl, naphtha-1-yl, benzimidazole-4-yl, 4-nitronapth-1-yl, and phenyl; and
R_2 = (C_1-C_4)alkyl.

12. The compound according to any one of claims 1-11, which is selected from the following:

(a) (2*R*,8a*RS*)-2-[4-[4-(Naphth-1-yl)-2-methylpiperazin-1-yl]butyl]-1,4-dioxoperhydropyrrolo[1,2-*a*]pyrazine;
(b) (2*S*,8a*RS*)-2-[4-[4-(Naphth-1-yl)-2-methylpiperazin-1-yl]butyl]-1,4-dioxoperhydropyrrolo[1,2-*a*]pyrazine;
(c) (2*R*,8a*R*)-2-[[4-(Naphth-1-yl)-2-methylpiperazin-1-yl]methyl]-1,4-dioxoperhydropyrrolo[1,2-*a*]pyrazine;
(d) (2*S*,8a*S*)-2-[[4-(Naphth-1-yl)-2-methylpiperazin-1-yl]methyl]-1,4-dioxoperhydropyrrolo[1,2-*a*]pyrazine;
(e) (2*R*,8a*S*)-2-[[4-(Naphth-1-yl)-2-methylpiperazin-1-yl]methyl]-1,4-dioxoperhydropyrrolo[1,2-*a*]pyrazine;
(f) (2*S*,8a*R*)-2-[[4-(Naphth-1-yl)-2-methylpiperazin-1-yl]methyl]-1,4-dioxoperhydropyrrolo[1,2-*a*]pyrazine;

(i) (2*R*,7a*RS*)-(-)-2-[3-[4-(3-Chlorophenyl)-2-methylpiperazin-1-yl]propyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole;
(j) (2*S*,7a*RS*)-(+)-2-[3-[4-(3-Methoxyphenyl)-2-methylpiperazin-1-yl]propyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole;
(k) (2*S*,7a*RS*)-(-)-2-[3-[4-(1-Benzofuran-7-yl)-2-methylpiperazin-1-yl]propyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole;
(l) (2*R*,7a*RS*)-(-)-2-[4-[2-Ethyl-4-(naphth-1-yl)piperazin-1-yl]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole;
(m) (2*R*,7a*RS*)-(-)-2-[4-[4-(Benzimidazol-4-yl)-2-methylpiperazin-1-yl]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole;
(n) 2*S*,7a*RS*)-(+)-2-[4-[4-(1-Benzofuran-7-yl)-2-methylpiperazin-1-yl]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole;
(o) (2*R*,7a*RS*)-(-)-2-[4-[2-Ethyl-4-(3-methoxyphenyl)piperazin-1-yl]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole;
(p) (2*S*,7a*RS*)-(+)-2-[4-[2-Methyl-4-(4-methylnaphth-1-yl)piperazin-1-yl]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole;
(q) (2*S*,7a*RS*)-(+)-2-[4-[2-Methyl-4-phenylpiperazin-1-yl]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole;
(r) (2*S*,7a*RS*)-(+)-2-[4-[4-(Benzimidazol-4-yl)-2-methylpiperazin-1-yl]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole;
(s) (2*S*,7a*RS*)-(+)-2-[4-[2-Methyl-4-(4-nitronaphth-1-yl)piperazin-1-yl]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole.

13. The compound according to claim 12, which is selected from the following:

(a) (2*R*,8a*RS*)-2-[4-[4-(Naphth-1-yl)-2-methylpiperazin-1-yl]butyl]-1,4-dioxoperhydropyrrolo[1,2-*a*]pyrazine;
(b) (2*S*,8a*RS*)-2-[4-[4-(Naphth-1-yl)-2-methylpiperazin-1-yl]butyl]-1,4-dioxoperhydropyrrolo[1,2-*a*]pyrazine;
(c) (2*R*,8a*R*)-2-[[4-(Naphth-1-yl)-2-methylpiperazin-1-yl]methyl]-1,4-dioxoperhydropyrrolo[1,2-*a*]pyrazine;
(d) (2*S*,8a*S*)-2-[[4-(Naphth-1-yl)-2-methylpiperazin-1-yl]methyl]-1,4-dioxoperhydropyrrolo[1,2-*a*]pyrazine;
(e) (2*R*,8a*S*)-2-[[4-(Naphth-1-yl)-2-methylpiperazin-1-yl]methyl]-1,4-dioxoperhydropyrrolo[1,2-*a*]pyrazine;
(f) (2*S*,8a*R*)-2-[[4-(Naphth-1-yl)-2-methylpiperazin-1-yl]methyl]-1,4-

dioxoperhydropyrrolo[1,2-*a*]pyrazine.

14. A compound which is selected from the following:

(g) 2-[4-[4-(Naphth-1-yl)piperazin-1-yl]butyl]-1,4-dioxoperhydropyrrolo[1,2-*a*]pyrazine;
(h) 2-[4-[4-(3,4-Dihydro-2*H*-1,5-benzodioxepin-6-yl)piperazin-1-yl]butyl]-1,4-dioxoperhydropyrrolo[1,2-*a*]pyrazine.

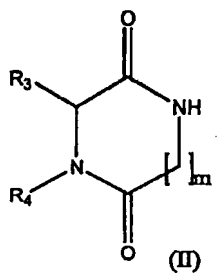
15. A pharmaceutical composition comprising an effective amount of a compound of formula Ia, their stereoisomers, N-oxides, crystalline forms, hydrates, pharmaceutically acceptable salts, pharmaceutically acceptable solvates or mixtures according to any of claims 1 to 14, in combination with one or more pharmaceutically acceptable carriers.

16. Use of a compound according to any of claims 1 to 14, for the manufacture of a medicament for the treatment and prophylaxis of a very wide range of disorders mediated by 5-HT_{1A} receptors and associated clinical symptoms in a human person.

17. The use according to claim 16, wherein such disorders are selected from Parkinson Disease, cerebral damage by thromboembolic ictus, craneoencephalic traumatisms, depression, migraine, pain, psychosis, anxiety disorders, aggressive disorders or urinary tract disorders.

18. A process for the preparation of compounds of formula Ia according to any of claims 1 to 14, which comprises one of the following:

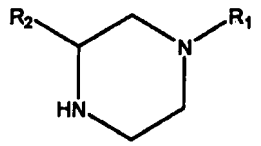
i) reacting a compound of formula II



(II)

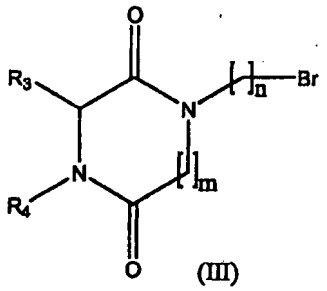
wherein m, R_3 and R_4 are as defined in claim 1;

with a compound of formula (IV)



(IV)

wherein R_1 and R_2 are as defined in claim 1;
resulting in final products of formula Ia wherein n = 1;
or
ii) reacting a compound of formula (III)



(III)

wherein R_3, R_4 and m are as defined in claim 1; and n > 1;
with a compound of formula (IV) as defined above;
resulting in final products of formula Ia wherein n > 1;
or

iii) acidifying a basic compound of formula Ia with a pharmaceutically acceptable acid to give a pharmaceutically acceptable salt;
or

iv) separating a mixture of isomers of a compound of formula Ia to isolate one of such isomers substantially free from the other isomer.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2005/057175

A. CLASSIFICATION OF SUBJECT MATTER
A61K31/4985 C07D487/04 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 96/06846 A (UNIVERSIDAD COMPLUTENSE DE MADRID; LOPEZ RODRIGUEZ, MARIA LUZ; ROSADO) 7 March 1996 (1996-03-07) cited in the application claims 1,15	1-18
T	LOPEZ-RODRIGUEZ, MARIA L. ET AL: "Synthesis and Structure-Activity Relationships of a New Model of Arylpiperazines. 8.Computational Simulation of Ligand-Receptor Interaction of 5-HT1AR Agonists with Selectivity over .alpha.1-Adrenoceptors" JOURNAL OF MEDICINAL CHEMISTRY , 48(7), 2548-2558, 2005, XP002329484 the whole document	1-18

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the International filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the International filing date but later than the priority date claimed

"T" later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the International search	Date of mailing of the International search report
24 February 2006	03/03/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,	Pâwillan

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2005/057175

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	LOPEZ-RODRIGUEZ, MARIA L. ET AL: "Synthesis and structure-activity relationships of a new model of arylpiperazines. Part 7: Study of the influence of lipophilic factors at the terminal amide fragment on 5-HT1A affinity/selectivity" BIOORGANIC & MEDICINAL CHEMISTRY , 12(6), 1551-1557, 2004, XP002329485 the whole document	1-18
Y	LOPEZ-RODRIGUEZ, MARIA L. ET AL: "Synthesis and Structure-Activity Relationships of a New Model of Arylpiperazines. 6. Study of the 5-HT1A/.alpha.1-Adrenergic Receptor Affinity by Classical Hansch Analysis, Artificial Neural Networks, and Computational Simulation of Ligand Recognition" JOURNAL OF MEDICINAL CHEMISTRY , 44(2), 198-207, 2001, XP002329486 the whole document	1-18
Y	LOPEZ-RODRIGUEZ, MARIA L. ET AL: "Synthesis and Structure-Activity Relationships of a New Model of Arylpiperazines. 5." JOURNAL OF MEDICINAL CHEMISTRY , 44, 186-197, 2001, XP002329487 cited in the application the whole document	1-18
Y	LOPEZ-RODRIGUEZ, MARIA L. ET AL: "Synthesis and Structure-Activity Relationships of a New Model of Arylpiperazines. 4." JOURNAL OF MEDICINAL CHEMISTRY , 42, 36-49, 1999, XP002329488 the whole document	1-18
Y	LOPEZ-RODRIGUEZ, MARIA L. ET AL: "Synthesis and Structure-Activity Relationships of a New Model of Arylpiperazines. 3. 2-'.omega.-(4-Arylpiperazin-1-yl)alkyl!perhydropyrrolo'1,2-c!imidazol s and -perhydroimidazo'1,5- a!pyridines: Study of the Influence of the Terminal Amide Fragment on 5-HT1A Affinity/Selectivity" JOURNAL OF MEDICINAL CHEMISTRY , 40(16), 2653-2656, 1997, XP002329489 the whole document	1-18

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2005/057175

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	LOPEZ-RODRIGUEZ, MARIA L. ET AL: "Synthesis and Structure-Activity Relationships of a New Model of Arylpiperazines. 2. Three-Dimensional Quantitative Structure-Activity Relationships of Hydantoin-Phenylpiperazine Derivatives with Affinity for 5-HT1A and .alpha.1 Receptors. A Comparison of CoMFA Models" JOURNAL OF MEDICINAL CHEMISTRY , 40(11), 1648-1656, 1997, XP002329490 the whole document	1-18
Y	LOPEZ-RODRIGUEZ, MARIA L. ET AL: "Synthesis and Structure-Activity Relationships of a New Model of Arylpiperazines. 1. 2-''4-(o-Methoxyphenyl)piperazin-1-yl!methyl!-1,3-dioxoperhydroimidazo'1,5-a!pyridine: A Selective 5-HT1A Receptor Agonist" JOURNAL OF MEDICINAL CHEMISTRY , 39(22), 4439-4450, 1996, XP002329491 cited in the application the whole document	1-18
Y	LOPEZ-RODRIGUEZ, MARIA L. ET AL: "Design and synthesis of S-(-)-2-''4-(napht-1-yl)piperazin-1-yl!methyl!-1,4-dioxoperhydropyrrolo'1,2-a!pyrazine (CSP-2503) using computational simulation. A 5-HT1A receptor agonist" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS , 13(8), 1429-1432, 2003, XP002329492 cited in the application the whole document	1-18

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2005/057175

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9606846 A	07-03-1996	AU 3079295 A	22-03-1996